Am. J. Hum. Genet. 44:806–810, 1989

Occupational Hydrocarbon Exposure among Fathers of Prader-Willi Syndrome Patients With and Without Deletions of 15q

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Summary

Prader-Willi syndrome (PWS) is a multiple-anomaly disorder in which 50%–70% of cases are associated with a de novo interstitial deletion [del 15(q11–13)] on prometaphase cytogenetic analysis, the remainder having apparently normal chromosomes. In most instances, the paternally derived chromosome has become deleted in the affected child, suggesting the possibility of a predisposing environmental factor. Strakowski and Butler found an increased incidence of paternal periconceptional employment in hydrocarbon-exposing occupations in this population. This observation may suggest a causal relationship to PWS. To determine whether this association may distinguish the cytogenetically different groups, we identified 81 patients with the disorder who were physically and cytogenetically examined in three centers, and we compared the frequency of possible periconceptional occupational hydrocarbon exposure between fathers of patients who demonstrate a 15q deletion and those who do not. There was no statistically significant difference between the cytogenetically different groups. In both groups, approximately half of the fathers had been employed in hydrocarbon-exposing jobs. These findings suggest lack of etiologic heterogeneity between the cytogenetically different groups for PWS and affirm the need to seek submicroscopic deletions through molecular genetic studies. These data also provide additional evidence that hydrocarbon exposure among fathers of children with PWS may be causally related to the disorder, and they also suggest the need for more accurate assessment of exposure via a large, controlled study.

Introduction

Prader-Willi syndrome (PWS) is a complex multisystem disorder whose major features include infantile hypotonia leading to feeding problems and failure to thrive, hypothalamic hypogonadotrophic hypogonadism causing genital hypoplasia and pubertal insufficiency, developmental delay and mental deficiency, early-childhood-onset obesity, behavior disorder, dysmorphic facial features, small hands and feet, and short stature (Cassidy 1984). In 1981 Ledbetter and co-workers found an interstitial deletion of chromosome 15q [del 15 (q11-q13)] by prometaphase chromosome analysis in some but not all individuals with PWS (Ledbetter et al. 1981, 1982). Subsequent studies have shown that 50%–70% of patients with the clinical signs and history for PWS have this interstitial deletion, with most of the remainder having apparently normal chromosomes by this technique (Ledbetter and Cassidy 1988). The possibility that those without an apparent deletion have submicroscopic deletions is currently being investigated using molecular genetic techniques. In nearly all studied cases involving an interstitial deletion (reviewed in Ledbetter and Cassidy 1988), parental chromosomes have been normal, indicating that the deletion is de novo. No factors predisposing to either this or other de novo deletions have been identified. Examination of the patients' and parents' chromosomes for polymorphisms has indicated that in 85%–100% of cases the deletion of PWS occurs in the paternally derived member of the

Received December 5, 1988; revision received February 7, 1989.

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0002-9297/89/4406-0005$02.00

chromosome 15 pair (Butler and Palmer 1983; Niikawa and Ishikiriyama 1985; Magenis 1988).

Male gonads are more exposed than those of the female, since they are located outside the body. For this reason, and because of the high rate of gametogenesis in the male, environmental effects are believed to be more likely to affect paternal gametogenesis (Magenis 1988). To seek possible environmental factors predisposing to PWS, Strakowski and Butler (1987) determined the frequency of lead- or hydrocarbon-exposing occupations among the fathers at conception of patients with PWS. This was compared with the occupations of fathers of children who have fragile X syndrome or Down syndrome. Their study involved utilization of existing support-group registries of information, based on questionnaires to families. The likelihood that a given occupation exposed the employee to lead or hydrocarbons was based on job classification, as published in previous similar studies (Kantor et al. 1979; Gold et al. 1982). Of 652 families affected by PWS and for whom information was available about paternal occupation at the time of conception of the affected child, 20.8% worked in occupations that are reported as having a high likelihood of exposing the employee to hydrocarbons, compared with 12.0% of fathers of 66 patients with fragile X syndrome and of 268 patients with Down syndrome.

Since there is a possibility that this environmental exposure may be etiologically related to the chromosomal abnormality associated with PWS, we sought to determine whether there was a difference in the rate of occupational exposure to hydrocarbons at the time of conception between fathers of children with PWS who have a 15q deletion and those children who do not have a deletion.

Methods

The patients with PWS who were included in this study were all examined by one of two of the coauthors (S.B.C. or M.G.B.), both clinical geneticists. All patients satisfied strict diagnostic criteria for PWS (Cassidy 1984), and all had chromosome analysis utilizing synchronization techniques and/or actinomycin D pretreatment for high resolution (Yunis 1976; Yu et al. 1981; Rybak et al. 1982; Butler et al. 1987). Chromosomes were banded with the GTG method and were analyzed at the 550–850-band level. The deletion status of chromosome 15 was determined after the analysis of at least 20 cells.

In some cases, information concerning parental occupations at the time of conception of the child with PWS was available from the initial evaluation. If it was not, one of the parents was contacted by telephone to obtain the information. In both groups, only the type of occupation was obtained. Occupations were categorized as being hydrocarbon exposing or not hydrocarbon exposing solely on the basis of job classification and by utilizing published studies as to whether an occupation was exposing or not (Kantor et al. 1979; Gold et al. 1982). No attempt was made to determine actual extent of exposure of individuals. It is not possible to determine whether any of the patients in this study were also included in the study by Strakowski and Butler (1987), since it would represent a breach of confidentiality to obtain patient names from the national registry. However, since the registry used by those authors included the entire United States and Canada, whereas the subjects for the current study represented only three centers, the overlap is likely to be small.

Clinical, cytogenetic, and occupational information was available for a total of 81 patients, of whom 35 were from the University of Connecticut (seen by S.B.C.) and 46 were from Indiana University or Vanderbilt University (seen by M.G.B.). Fifty-three (65%) of the 81 patients had an interstitial deletion at 15(q11–13), and the remainder had apparently normal chromosomes. Statistical analysis was performed using χ^2 testing and the Miettienen (1976) test-based method.

Results

The results of the survey are shown in table 1. Of the 53 fathers of children with 15q deletions, 24 (45%) were engaged in potentially hydrocarbon-exposing occupations, as were 15 (54%) of the 28 fathers of children with apparently normal chromosomes. The difference between these two numbers was not statistically significant ($\chi^2 = 0.498$, $P = .48$). The odds ratio was 0.72, with a 95% confidence interval of 0.28–1.81. The average age of PWS patients with a deletion was 14.8 years (range 0.5–35 years), and the average age of those without a deletion was 13.4 years (range 1–45 years).

Table 1

Paternal Occupational Hydrocarbon Exposure at Conception of a Child with Prader-Willi Syndrome

	Exposed	Unexposed	Total
Deletion 15q	24	29	53
Nondeleted	15	13	28
Total	39	42	81

Overall, at the time of conception of children with PWS, 39 (48%) of the 81 fathers were employed in occupations that are considered to carry a high risk of exposing them to hydrocarbons. There was no difference in the magnitude of this percentage between the patients ascertained at the two centers. This percentage is statistically significantly different from the 12% reported by Strakowski and Butler (1987) for the fathers of 268 children with Down syndrome and of 66 children with fragile X syndrome ($\chi^2 = 55.34$, $P < .001$). In the study by Kantor et al. (1979), utilizing birth certificate data, only 7% of 149 fathers of children in Connecticut who were age matched with children who had developed Wilms tumor were employed in occupations that are considered hydrocarbon-exposing. The difference between those data and the data for PWS (48%) was highly statistically significant as well ($\chi^2 = 53.75$, $P < .001$).

The actual occupations of the fathers are listed in table 2.

Discussion

This study was designed to examine whether the frequency of periconceptional occupation in hydrocarbon-exposing environments differs between fathers of carefully diagnosed and cytogenetically analyzed children with PWS who do have a 15q deletion and those who do not have a 15q deletion. The results reveal no significant difference between them. If hydrocarbons

Table 2

Occupations of Fathers at Conception of Children with Prader-Willi Syndrome

Occupation	Deletion	Nondeletion
Exposing:		
Motor vehicle driver/airline pilot	3	3
Motor mechanic	0	1
Engine room worker on ship	0	1
Gas station worker	1	2
Chemist/technician—industrial	5	2
Furniture refinisher/lacquer sprayer	3	1
Painter/auto painter	2	1
Machinist	3	1
Tool/dye maker	4	2
Press operator	1	0
Factory worker	2	0
Machine repairer	0	1
Total	24	15
Nonexposing:		
Office worker/writer/lawyer	9	3
Teacher	3	0
Physicist	1	0
Salesman (not traveling)	1	3
Medical worker (physician, orderly)	2	1
Military	2	0
Maintenance	3	1
Engineer (safety, electrical, tooling)	2	1
Grocery clerk	2	0
Policeman	1	0
Welder	1	0
Telephone repairer	1	0
Farmer	0	1
Garage foreman	1	0
Cook	0	1
Railroad switchman	0	1
Unemployed	0	1
Total	29	13

are etiologically related to PWS, these data are consistent with the suggestion, which is based on lack of significant clinical heterogeneity, that those patients without apparent chromosome abnormalities might have submicroscopic deletions as the cause of PWS. If a causal relationship is assumed, one would expect that the alternative possibility—namely, that there is etiologic heterogeneity in PWS between those with and without a deletion—would lead to a difference in the paternal hydrocarbon exposure rate. The lack of difference in paternal hydrocarbon exposure rate is consistent with the observed absence of significant clinical differences between these two groups of patients with PWS (e.g., see Butler et al. 1986; Labidi and Cassidy 1986). The present study thus provides additional support for research utilizing multiple DNA probes for the 15q region which is deleted in the majority of cases of PWS, so that smaller, less visible deletions of genetic material can be sought. This research is ongoing in a number of laboratories.

The present study has also provided additional evidence that there may be a high incidence of hydrocarbon exposure of the fathers at or around the time of conception of children with PWS, an incidence statistically significantly higher than that in two published control groups (Kantor et al. 1979; Strakowski and Butler 1987). The data presented here must be interpreted with caution for a number of reasons. First, since the study was designed to compare two groups of patients with PWS (i.e., patients with and patients without del 15q), the study design did not include an appropriate control group for examining incidence of potential hydrocarbon exposure among fathers. Recollection of occupations may also be inaccurate, since the patients themselves ranged in age from 6 mo to 45 years, although there was no significant difference between the average ages of the deletion and nondeletion patients. Bias and inaccuracy may have been introduced by the method of obtaining occupation type (sometimes from medical records, sometimes from telephone interview with father, sometimes with mother). In addition, bias could have been introduced because the study was not done in a blinded fashion, though this source of bias is unlikely. Misclassification of exposure category could have resulted from lack of information about actual individual exposure to hydrocarbons, since only paternal occupation was sought, with the likelihood of hydrocarbon exposure relying upon published studies of occupations. Another limitation of the study is that no information was obtained about exposure to hydrocarbons outside the workplace.

Chromosome aberrations have been reported in subjects occupationally exposed to hydrocarbons such as paint (Haglund et al. 1980), toluene (Mäki-Paakkanen et al. 1980; Bauchinger et al. 1982), and vinyl chloride (Hansteen et al. 1978; Kucerová et al. 1979), to name only a few. Whether hydrocarbon exposure is also a potential cause of chromosomal deletions leading to PWS, or whether such exposures may lead to other de novo chromosomal deletion or breakage syndromes, cannot be definitively ascertained from either this study or that of Strakowski and Butler (1987), since both are preliminary owing to methological flaws. However, the data from these two studies are sufficiently suggestive to warrant further, more detailed studies. Such studies may help determine whether environmental hazards play a role in causing this condition—and, possibly, other conditions associated with chromosomal deletions, since these are also largely of paternal origin (Magenis 1988). If so, this would represent the first identification of an environmental factor producing paternally related events as a cause for genetic aberrations.

Acknowledgment

The authors wish to thank Pilar Echeverria for secretarial assistance.

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